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Article

A 2D-QSPR approach to predict blood-brain barrier penetration of drugs acting on the central nervous system

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Drugs acting on the central nervous system (CNS) have to cross the blood-brain barrier (BBB) in order to perform their pharmacological actions. Passive BBB diffusion can be partially expressed by the blood/brain partition coefficient (logBB). As the experimental evaluation of logBB is time and cost consuming, theoretical methods such as quantitative structure-property relationships (QSPR) can be useful to predict logBB values. In this study, a 2D-QSPR approach was applied to a set of 28 drugs acting on the CNS, using the logBB property as biological data. The best QSPR model [n = 21, $r = 0.94$ ($r^2 = 0.88$), $s = 0.28$, and $Q^2 = 0.82$] presented three molecular descriptors: calculated *n*-octanol/water partition coefficient (ClogP), polar surface area (PSA), and polarizability (α). Six out of the seven compounds from the test set were well predicted, which corresponds to good external predictability (85.7%). These findings can be helpful to guide future approaches regarding those molecular descriptors which must be considered for estimating the logBB property, and also for predicting the BBB crossing ability for molecules structurally related to the investigated set.

Uniterms: Two-dimensional quantitative structure-property relationships (2D-QSPR). Calculated *n*-octanol/water partition coefficient (ClogP). Blood-brain barrier. Benzodiazepines.

Fármacos que atuam no sistema nervoso central (SNC) devem atravessar a barreira hematoencefálica (BHE) para exercerem suas ações farmacológicas. A difusão passiva através da BHE pode ser parcialmente expressa pelo coeficiente de partição entre os compartimentos encefálico e sanguíneo (logBB, *brain/blood partition coefficient*). Considerando-se que a avaliação experimental de logBB é dispendiosa e demorada, métodos teóricos como estudos das relações entre estrutura química e propriedade (QSPR, *Quantitative Structure-Property Relationships*) podem ser utilizados na previsão dos valores de logBB. Neste estudo, uma abordagem de QSPR-2D foi aplicada a um conjunto de 28 moléculas com ação central, usando logBB como propriedade biológica. O melhor modelo de QSPR [n = 21, $r = 0{,}94$ ($r^2 = 0{,}88$), $s = 0{,}28$ e $Q^2 = 0{,}82$] apresentou três descritores moleculares: o coeficiente calculado de partição *n*-octanol/água (ClogP), área de superfície polar (PSA) e polarizabilidade (α). Seis dos sete compostos do conjunto de avaliação foram bem previstos pelo modelo, o que corresponde a um bom poder de previsão externa (85,7%). Os resultados obtidos podem auxiliar de forma relevante em estudos futuros, orientando quais descritores moleculares devem ser considerados para estimar logBB e prever a passagem através da BHE de moléculas estruturalmente relacionadas às do conjunto investigado.

Unitermos: Relações quantitativas bidimensionais entre estrutura química e propriedade (2D-QSPR). Coeficiente calculado de partição *n*-octanol/água (ClogP). Barreira hematoencefálica. Benzodiazepínicos.

INTRODUCTION

The distribution of many drugs to the brain is significantly different from that occurring in other organs, owing to the presence of the blood-brain barrier (BBB). This consists of a specialized system of capillary endothelial cells that protects the brain against harmful substances in the blood stream, while supplies this organ with the required nutrients for its proper functions (Escuder-Gilabert *et al.*, 2004).

The BBB plays an important role in maintaining homeostasis, separating the brain from systemic circulation.

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Its endothelial cells have tight junctions, promoting a very high transendothelial resistance (1500-2000 Ωcm²), preventing paracellular passage of hydrophilic solutes (Misra *et al.*, 2003). Furthermore, a number of neuroanatomical structures, including catabolic enzymes, efflux transporters and astrocytes prolongations, provide a restricted diffusion of chemical compounds through the brain (Misra *et al.*, 2003; Hitchcock, 2008; Habgood *et al.*, 2000).

Passive diffusion through the BBB is the primary process of many therapeutic compounds' translocation from blood to brain. This step is one of the most critical pharmacokinetic issues in the designing of drug candidates for action on the Central Nervous System (CNS). If the drug cannot cross the BBB, no biological effect in the CNS is observed. This penetration is also a concern in the development of other classes of drugs, for which penetration through the BBB could result in toxicity due to undesirable effects on nervous tissues (Li *et al.*, 2005; Katritzky *et al.*, 2006).

Although some drugs use transporters, most of them can enter the brain by passive diffusion through the endothelial cells. One of the main important drug properties governing passive diffusions is lipophilicity. In general, the more lipid soluble the molecule, the more easily it will move from the blood to the brain, crossing the endothelial cell membranes. Lipophilicity can be expressed by the *n*-octanol/water partition coefficient (logP), which represents the relative affinity of a molecule between organic and aqueous media (Misra *et al.*, 2003; Habgood *et al.*, 2000; Goodwin *et al.*, 2005). Other important molecular features, considering passive diffusion, include molecular size (with a cut-off value of 400-700 Da) and intermolecular interaction forces (which express the relative affinity to lipophilic or hydrophilic solvent) (Habgood *et al.*, 2000; Misra *et al.*, 2003; Iyer *et al.*, 2002).

The relative affinity of a molecule between blood and brain can be expressed in terms of the blood/brain partition coefficient (logBB), according to Equation 1:

$$\log BB = \log\left(\frac{C_{brain}}{C_{blood}}\right) \qquad (1)$$

In Equation 1, C_{brain} and C_{blood} are the equilibrium concentrations of a molecule in the brain and the blood, respectively (Katritzky *et al.*, 2006). However, this experimental determination is time and cost consuming, preventing extended applications. Therefore, computer-assisted drug design methodologies (CADD), such as quantitative structure-property and/or structure-activity relationship studies (QSPR and QSAR, respectively), may help to estimate biological data, reducing synthetic steps, predicting pharmacokinetic and pharmacodynamic profiles, constituting an important tool in the design and development of new drugs and novel leads (Katritzky *et al.*, 2006). A literature review reported several studies, carried out on a number of different chemical structures, and in which 2D and 3D QSPR models have been proposed to predict logBB values (Katritzky *et al.*, 2006; Van Damme *et al.*, 2008; Iyer *et al.*, 2002; Konovalov *et al.*, 2007; Subramanian *et al.*, 2003; Zhao *et al.*, 2007; Zhang *et al.*, 2008; Narayanan *et al.*, 2005). Some of these models show a correlation between logBB and some physicochemical parameters, such as molecular refractivity (MR), molecular volume (V), acid ionization constant (K_a and pK_a), thermodynamic parameters (solvation energy, etc.), polar surface area (PSA), and others. (Chen *et al.*, 2009; Clark, 1999). Nevertheless, easy interpretable mathematical models, with good internal and external predictability, are still needed for some specific drug classes. Against this background, in the present study a two-dimensional (2D) QSPR approach was applied to a set of 28 structurally similar molecules including benzodiazepines, tricyclic compounds and their metabolites, with CNS activity as antidepressant and neuroleptic, in order to build a QSPR model able to predict logBB values and also provide relevant findings about the BBB crossing ability of other compounds structurally related to the investigated set.

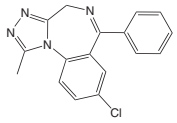
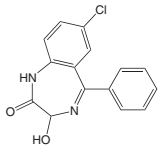
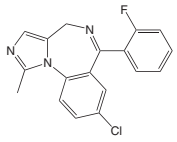
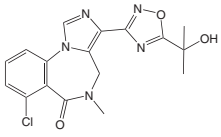
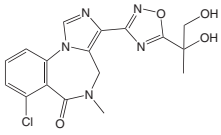
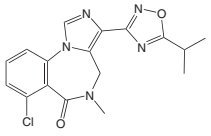
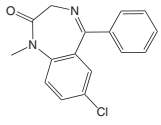
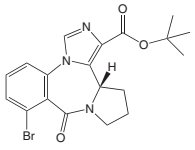
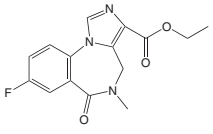
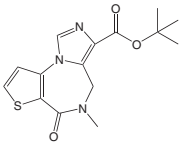
MATERIAL AND METHODS

A set of 28 molecules, including benzodiazepines, tricyclic compounds and their metabolites, were selected from Katritzky *et al.* (Katritzky *el al.*, 2006). Their structural similarity is based on the presence of an azepine or isosteric ring bound to at least one aromatic ring. The experimental logBB values were assessed using animal models and synthesized radio-labeled compounds. Often, this measure is based on the degree of BBB penetration, defined as the ratio of the steady-state molar concentration of the drug molecule (radio-labeled) in the brain and in the blood (Katritzky *et al.*, 2006). The logBB values are given in Table 1, comprising the dependent variables of this QSPR analysis. The range of logBB values is from -1.82 to 1.20.

The molecules were randomly divided into two sets. The training set was composed of 21 compounds whereas seven compounds were used for the external validation (test set). The test set compounds were not included in the development of the 2D-QSPR models.

The three-dimensional structures of each of the 28 molecules were built in their neutral forms employing the HyperChem 7.51 software (Hypercube Inc., 2003). The

TABLE I - Chemical structures and logBB experimental values (logBBexp) found for training and test sets (Katritzky *et al.*, 2006). The test set compounds are marked with an asterisk (*)

Compounds	Structure	$logBB_{exp}$
1. alprazolam		0.04
2. oxazepam		0.61
3. midazolam		0.36
4. M1-L663-581		-1.34
5. M2-L663-581		-1.82
6. L663-581		-0.30
7. diazepam		0.52
8. bretazenil		-0.09
9. flumazenil		-0.29
10. Ro 19-4603		-0.25

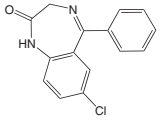
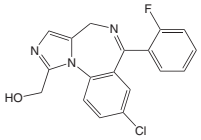
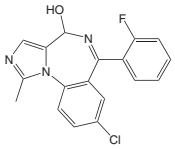
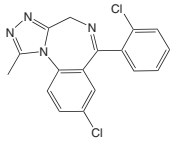
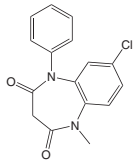
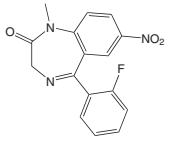
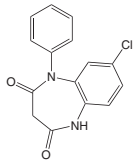
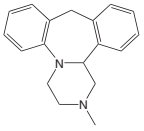
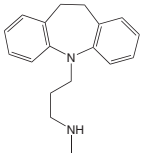
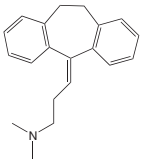
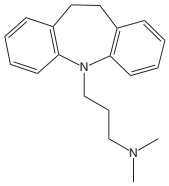
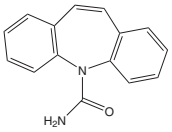
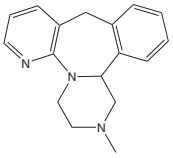
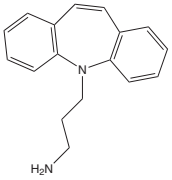
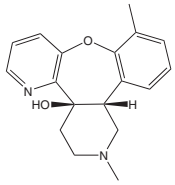
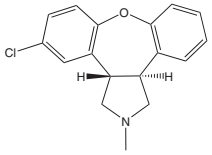
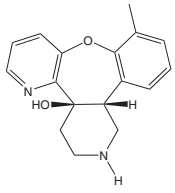
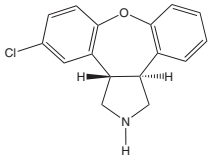
Compounds	Structure	$logBB_{exp}$
11. demethyldiazepam		0.50
12. 1-OH-midazolam		-0.07
13. 4-OH-midazolam		-0.30
14. triazolam		0.74
15. clobazam		0.35
16. flunitrazepam		0.06
17. demethylclobazam		0.36
18. mianserin		0.99
19. desipramine		1.20

TABLE I - Chemical structures and logBB experimental values (logBBexp) found for training and test sets (Katritzky *et al.*, 2006). The test set compounds are marked with an asterisk (*) (cont.)

Compounds	Structure	$logBB_{exp}$
20. amitriptyline		0.98
21. imipramine		0.83
22. carbamazepine*		0.00
23. mirtazapine*		0.53
24. *N*-demethyl desipramine*		1.06
25. ORG4428*		0.82
26. ORG5222*		1.03
27. ORG32104*		0.52
28. ORG30526*		0.39

crystallized structures of the drugs diazepam and imipramine were retrieved from the Protein Data Bank (PDB) (Bernstein *et al.*, 1977) [entry codes 2bxf, resolution 2.95 Å (Ghuman *et al.*, 2005); and 2q72, resolution 1.70 Å (Singh *et al.*, 2007)] and used as the starting geometries to construct all benzodiazepines and tricyclic compounds, respectively. Each 3D-model had its geometry optimized by HyperChem 7.51, using MM+ force field without any restriction (Allinger, 1977), followed by the AM1 semiempirical quantum method (Dewar *et al.*, 1985). Partial atomic charges were calculated using the AM1 semiempirical method, also implemented by the HyperChem 7.51 program (Hypercube Inc, 2003).

As mentioned above, the structures modeled were used to calculate the molecular descriptors or independent variables used in this study, employing HyperChem 7.51 (Hypercube Inc, 2003) and MarvinBeans 4.1.8 software (ChemAxon Ltd, 1998-2009) (see Table II).

A preliminary systematic search of the most significant independent variables was carried out based on their distribution or variability against the biological property (visual inspections) using scatter plots [Pirouette® 3.11 (Infometrix, Inc., 1990-2003)]. Therefore, the scatter plots of logBB *versus* the calculated molecular descriptors aided in the decision concerning which molecular descriptors would be more relevant in describing the biological property.

TABLE II - Molecular descriptors calculated using HyperChem® 7.51 and MarvinBeans 4.1.8 software

Software	**Molecular Descriptors**
HyperChem® 7.51	solvent-accessible surface area (Aprox.), solvent-accessible surface area (Grid), van der Waals volume, solvent-accessible volume.
MarvinBeans 4.1.8	ClogP, polarizability (α), polar surface area (PSA), H-bond donor, H-bond acceptor, molar refractivity (MR)

The selected descriptors were used to build the 2D-QSPR models employing multiple linear regression (MLR) and leave-one-out (LOO) cross-validation method, performed by BuildQSAR® 1.0.0 software (Oliveira, Gaudio, 2003). Due to the relatively small size of the training set (n = 21), the statistical restriction which imposes a limit from four up to five observations (compounds) per descriptor or independent variable (Ferreira, 2002; Tavares, 2004) were respected in this approach and a maximum of four molecular descriptors per model was considered.

Statistical measures of significance including the LOO cross-validation coefficient (Q^2), linear regression coefficient (r or r^2), standard deviation (s), Fischer's value (F) and standard predictive residual sum of squares value (s_{PRESS}) were used to evaluate the robustness of the QSPR models. Moreover, a linear cross-correlation matrix of the descriptors was computed to verify if the independent variables were correlated to one another or otherwise. Pairs of descriptors which are highly correlated ($R \approx 1$) to one another are deemed to provide nearly the same information to the model, while poorly correlated pairs of descriptors ($R < 0.5$) give distinct contribution to the model.

The differences between the experimental or observed ($logBB_{exp}$) and calculated or predicted ($logBB_{pred}$) properties are called residual values. In this study, the compounds of the training set for which the absolute residual values exceeded two standard deviation (SD) from the mean of a model, were considered as outliers. This threshold corresponds to a significance level of ninety-five percent (Ferreira *et al.*, 1999).

As mentioned previously, the seven compounds of the test set were not included in the build of the QSPR models, but were used to validate the best QSPR model constructed from the training set, and to evaluate its prediction capacity. The predicted logBB value of each compound in the test set was calculated using the equation of the best model by substitution of the molecular descriptors' calculated values. The absolute residual values should not be higher than one SD from the mean of the model, which corresponds to a significance level of ninety-nine percent.

RESULTS AND DISCUSSION

Molecular descriptor selection

The proper selection of molecular descriptors, i.e., those truly relevant in describing the studied property or biological activity, is a challenge in QSPR/QSAR studies, since the amount of information generated by the available software is sometimes enormous and hard to comprehend (van de Waterbeemd, Rose, 2008). In this study, the calculated molecular descriptors were related to lipophilicity (ClogP), intrinsic properties, such as molecular size and shape [volume (V), surface area] and electronic, topologic and mixed parameters [polarizability (α), number of H-bond acceptor and donor sites, polar surface area (PSA) and molar refractivity (MR)]. The polar surface area (PSA) calculation is defined as the sum of the surface of all the polar atoms of the molecule, especially N and O, including H atoms. The estimation of topological polar surface area (TPSA) was based on the method described by Ertl, 2000 (Ertl *et al.*, 2000). This method, implemented in MarvinBeans software (ChemAxon Ltd, 1998-2009), provides results which are practically identical to the 3D PSA, while the TPSA is approximately 100-times faster. Thus, the 2D representation is an approximation of the 3D PSA (Ertl, 2007).

As described in the Material and Methods Section, the scatter plots of logBB *versus* each of the calculated molecular descriptors were employed as preliminary selection criterion (data not shown). The most relevant independent variables, which were used to generate the QSPR models, presented a good dispersion of the data related to the variability of the biological property. Linear and non-linear tendencies were both considered. Only the number of H-bond acceptor and donor sites did not provide a suitable dispersion of data considering the variability of the logBB values and were therefore not included in the generation of the QSPR models.

2D-QSPR models

All the best fit models were linear given the ClogP values' range was not larger than four logarithmic units. Thus, parabolic or bilinear functions were not considered (Patrick, 2008). The resulting 2D-QSPR models are listed below.

Model 1:
logBB = +0.47 (±0.11)ClogP – 0.94 (±0.30)
$n = 21$; $r = 0.90$ ($r^2 = 0.81$); $s = 0.33$; $F = 80.04$; $Q^2 = 0.74$; $s_{PRESS} = 0.39$

Model 2:
logBB = -0.02 (±0.01)PSA + 1.23 (±0.32)
$n = 21$; $r = 0.89$ ($r^2 = 0.79$); $s = 0.35$; $F = 68.52$; $Q^2 = 0.72$; $s_{PRESS} = 0.40$

Model 3:
logBB = +0.28 (±0.24)ClogP – 0.01 (±0.01)PSA – 0.03 (±1.13)
$n = 21$; $r = 0.91$ ($r^2 = 0.83$); $s = 0.32$; $F = 45.90$; $Q^2 = 0.78$; $s_{PRESS} = 0.38$

Model 4:
logBB = +0.24 (±0.22)ClogP – 0.05 (±0.04)α – 0.01 (±0.01)PSA + 1.76 (±1.92)
$n = 21$; $r = 0.94$ ($r^2 = 0.88$); $s = 0.28$; $F = 39.74$; $Q^2 = 0.82$; $s_{PRESS} = 0.34$

Model 5:
logBB = +0.21 (±0.22)ClogP – 0.01 (±0.01)PSA – 0.03 (±0.01)MR + 1.41 (±1.54)
$n = 21$; $r = 0.94$ ($r^2 = 0.88$); $s = 0.28$; $F = 42.10$; $Q^2 = 0.83$; $s_{PRESS} = 0.33$

All the models presented *r* values higher than 0.8, indicating well fitting models. Models 4 and 5 had the highest *r* values (0.94; $r^2 = 0.88$) and the lowest *s* values (0.28). However, the *s* value is better evaluated when the dependent variable's standard deviation is also given, and should be smaller than the latter (Patrick, 2008). For logBB, specifically, the standard deviation is not currently reported (Abraham *et al.*, 2006).

The highest *F* values were obtained from models 1 and 2 (80.04 and 68.52, respectively). It is noteworthy that the *F* value decreases as the number of descriptors in the model increases, indicating a substantial loss of statistical significance. This is likely due to the total number of compounds in the training set ($n = 21$).

The internal predictability of a model is expressed by the LOO cross-validation correlation coefficient (Q^2), which is a very important statistical measure of QSPR/QSAR models. The Q^2 values for all models were higher than 0.5. Models 4 and 5 presented the highest Q^2 values (0.82 and 0.83, respectively).

Taking into account the evaluation of all statistical parameters measured, models 4 and 5 were considered the best QSPR models. Both equations presented three independent variables, but model 4 has α instead of MR. These two descriptors are indeed related to each other, since MR can express both steric and electronic effects. Hence, a linear cross-correlation matrix of the descriptors of models 4 and 5 was computed, using BuildQSAR® 1.0.0, to verify if the independent variables were correlated to one another or otherwise (see Table III). As mentioned previously, pairs of descriptors that are highly correlated ($R \approx 1$) to one another are deemed to provide nearly the same information to the model, while poorly correlated pairs of descriptors ($R < 0.5$) give distinct contribution to the model.

According to the results presented in Table 3, ClogP and PSA are highly correlated ($R = 0.82$), meaning they provide almost the same information to both models. However, this correlation value can be understood as a mathematical artifact since the parameters are not biologically correlated (the former represents a lipophilic parameter, while the latter is a topological descriptor). Moreover, the models presenting both parameters proved to be statistically more significant, indicating the importance of including ClogP and PSA in the same model. Furthermore, a previous study reported poor intercorrelation between these two data items ($R = 0.299$) (Ertl, 2007) reinforcing the mathematical artifact assumption. On the other hand, the MR and α presented a high correlation coefficient ($R = 0.84$) and are actually correlated. MR is a composite parameter that considers molecular volume and polarization capacity, whereas α represents the relative tendency of a molecular charge distribution to be distorted from its normal shape by an external electric field, which may be caused by the presence of an ion or dipole nearby (Ertl, 2007).

TABLE III - Linear cross-correlation matrix found for the molecular descriptors of models 4 and 5

	ClogP	α	PSA	MR
ClogP	**1.00**	0.06	0.82	0.26
α		**1.00**	0.03	0.84
PSA			**1.00**	0.20
MR				**1.00**

ClogP = calculated *n*-octanol/water partition coefficient; PSA = polar surface area; α = polarizability; MR = molar refractivity.

Therefore, models 4 and 5 have relevant independent variables describing the logBB property. The signs of the regression coefficients indicate the direction of the descriptors' contribution to the biological property. A positive sign can be interpreted as a favorable contribution to the biological property (ClogP) while a negative sign, as being unfavorable (PSA, α, MR).

Size and shape were not directly expressed in the 2D-QSPR models. Instead, some descriptors such as MR and PSA consider molecule size or shape in their calculation. Molecular refractivity (MR), as mentioned earlier, for example, considers both molecular volume (and indirectly size and shape) and molecule polarizability capability (Patrick, 2008). Polar surface area (PSA) is another example which considers topological parameters, taking into account the number of polar atoms (N, O and H) and is indirectly related to the size of the molecule (Ertl, 2007).

The internal predictability of models 4 and 5 was also explored as described in the Material and Methods section. The results are presented in Tables IV and V, respectively.

TABLE IV - Residual values found for model 4

Compounds	$logBB_{exp}$	$logBB_{pred}$	Residual Values ($logBB_{exp} - logBB_{pred}$)
1-OH-midazolam	-0.07	0.06	-0.13
4-OH-midazolam	-0.30	0.18	-0.48
alprazolam	0.04	0.17	-0.13
amitriptyline	0.98	1.06	-0.08
bretazenil	-0.09	-0.43	0.34
clobazam	0.35	0.40	-0.05
desipramine	1.20	0.84	0.36
demethylclobazam	0.36	0.46	-0.10
demethyldiazepam	0.50	0.69	-0.19
diazepam	0.52	0.63	-0.11
flumazenil	-0.29	-0.31	0.02
flunitrazepam	0.06	0.09	-0.03
Imipramine	0.83	0.92	-0.09
L663-581	-0.30	-0.46	0.16
M1L663-581	-1.34	-1.01	-0.33
M2L663-581	-1.82	-1.51	-0.32
mianserin	0.99	1.04	-0.05
midazolam	0.36	0.51	-0.15
oxazepam	0.61	0.40	0.21
Ro19-4603	-0.25	-0.69	0.44
triazolam	0.74	0.20	0.54
			SD = 0.26; 2SD = 0.52

Note: $logBB_{exp}$ = logBB experimental or observed; $logBB_{pred}$ = logBB predicted or calculated; SD = standard deviation; 2SD = two standard deviations.

According to Tables 4 and 5, only model 4 proved capable of predicting logBB for all compounds of the training set. The absolute residual values did not exceed two SDs from the mean of model 4, meaning there were no outliers. Thus, model 4 was selected as the best 2D-QSPR model.

External Validation

As outlined previously, model 4 was the best fit model selected to describe logBB in terms of ClogP, PSA and α. The external validation was performed using the test set ($n = 7$). The calculated molecular descriptors present in model 4, the experimental and calculated logBB values, the respective residual values as well as the SD values obtained from the test set compounds, are listed in Table VI.

Six out of the seven test set compounds were well predicted by model 4, corresponding to good external predictability (85.7 %). The residual value of the molecule ORG4428 was not considered statistically significant, since the difference was only in the second decimal. Moreover, the biological measurement of logBB is very susceptible to experimental errors.

The highest absolute residual value in the test set was observed for carbamazepine, which was the only molecule not well predicted by model 4. However, this drug penetration in the CNS is highly driven by several carriers, specifically the ABC family (ATP-binding cassette), such as the efflux protein P-gp (P-glycoprotein) (Sun *et al.*, 2006). In addition, its pharmacokinetic profile is very complex due to its limited water solubility and capacity of self metabolism induction (Charney *et al.*, 2006). Consequently, carbamazepine's BBB permeation is a composite of several mechanisms and the 2D-QSPR model proposed considers only passive crossing, resulting in differences between the experimental value (which considers all the mechanisms involved) and the predicted value.

TABLE V - Residual values found for model 5

Compounds	$logBB_{exp}$	$logBB_{pred}$	Residual Values ($logBB_{exp} - logBB_{pred}$)
1-OH-midazolam	-0.07	-1.65	1.58
4-OH-midazolam	-0.30	-1.53	1.23
alprazolam	0.04	-1.53	1.57
amitriptyline	0.98	-0.71	1.69
bretazenil	-0.09	-2.23	2.14
clobazam	0.35	-0.89	1.24
desipramine	1.20	-0.54	1.74
demethylclobazam	0.36	-0.83	1.19
demethyldiazepam	0.50	-0.63	1.13
diazepam	0.52	-0.68	1.20
flumazenil	-0.29	-1.84	1.55
flunitrazepam	0.06	-1.31	1.37
imipramine	0.83	-0.53	1.36
L663-581	-0.30	-2.51	2.21
M1L663-581	-1.34	-3.04	1.70
M2L663-581	-1.82	-3.52	1.70
mianserin	0.99	-0.35	1.34
midazolam	0.36	-1.22	1.58
oxazepam	0.61	-0.92	1.53
Ro19-4603	-0.25	-2.26	2.01
triazolam	0.74	-1.57	2.31
			SD = 0.35; 2SD = 0.69

Note: $logBB_{exp}$ = logBB experimental or observed; $logBB_{pred}$ = logBB predicted or calculated; SD = standard deviation; 2SD = two standard deviations.

TABLE VI - Molecular descriptors of the best QSPR model (model 4), the experimental and calculated logBB values, the residual values and the respective SD value found for the test set compounds

Compounds	ClogP	PSA (Å²)	α (Å³)	$logBB_{exp}$	$logBB_{pred}$	Residual Values ($logBB_{exp} - logBB_{pred}$)
carbamazepine	3.22	46.33	26.95	0.00	0.72	-0.72
mirtazepine	3.38	19.37	31.23	0.53	0.82	-0.29
N-demethyldesipramine	3.24	29.26	30.98	1.06	0.70	0.36
ORG4428	2.49	32.70	34.11	0.82	0.33	0.49
ORG5222	3.10	12.47	29.83	1.03	0.89	0.14
ORG32104	2.25	41.49	32.26	0.52	0.27	0.25
ORG30526	2.74	21.26	27.99	0.39	0.81	-0.42
						SD = 0.45

Note ClogP = calculated *n*-octanol/water partition coefficient; PSA = polar surface area; α = polarizability; $logBB_{exp}$ = logBB experimental or observed; $logBB_{pred}$ = logBB predicted or calculated; SD = standard deviation.

CONCLUSION

The present study employed a set of 21 molecules to build 2D-QSPR models in order to predict BBB passive permeation, i.e., the mechanism proposed is the passive diffusion of the molecules through the BBB. The whole approach and methodology are simple and easy to interpret. Nevertheless, the models obtained were robust

and presented suitable internal predictability. The best fit model (model 4) had three descriptors, ClogP, PSA and α, which are well-known parameters and strongly influence BBB passive crossing. It is known that lipophilicity is a determining factor in drugs pharmacokinetics, influencing biological membrane permeation. The ClogP contribution to the models was positive in all the cases, suggesting that lipophilic moieties, that increase this parameter, facilitate passive translocation. By contrast, polar moieties seem to restrict molecule entry to the CNS. Quantitatively, this behavior is expressed by PSA and α, which contribute negatively to BBB diffusion. Published data has described linear models to explain the passive crossing through the BBB. The lipophilic characteristic has been described as the main factor that drives the passive diffusion from the blood into the cells and, in this case, the crossing through the BBB. As stated previously, the literature also reports other important parameters that seem to be related to the blood-brain partition (logBB): capability of forming hydrogen bonds, molecular flexibility, ability to bind to the lipophilic membrane, acid ionization constant (K_a and pK_a), thermodynamic parameters (solvation energy, etc.), molecular refractivity (MR), molecular volume (V), polar surface area (PSA) and other electronic and topologic parameters. Nevertheless, the model presented in this study is comparable or better than other published 2D-QSAR BBB models and show similar descriptors used by other authors. (Norinder *et al*., 2002; Katritzky *et al.*, 2006; van Damme *et al.*, 2008; Iyer *et al.*, 2002; Konovalov *et al.*, 2007; Subramanian *et al.*, 2003; Zhao *et al.*, 2007; Zhang *et al.*, 2008; Narayanan *et al.*, 2005; Young *et al.*, 1988; Abraham, 2004; Goodwin *et al.*, 2005). These findings can help future decisions about which groups are favorable or otherwise for CNS entry by BBB permeation, based on the physicochemical properties evaluated here. Additionally, due to its excellent external predictability, the best fit model can be applied to predict the logBB property of other compounds with the same structural motif, such as an azepine or isosteric ring bound to at least one aromatic ring.

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